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=> d his

     (FILE 'HOME' ENTERED AT 21:37:18 ON 23 JAN 2003)

     FILE 'CAPLUS' ENTERED AT 21:37:27 ON 23 JAN 2003
L1            10 S MGLUR5(P)(INHIBIT? OR ANTAGONIST?) AND (ANXIETY OR ANXIOUS? O

     FILE 'REGISTRY' ENTERED AT 21:40:14 ON 23 JAN 2003
L2                STRUCTURE UPLOADED

     FILE 'STNGUIDE' ENTERED AT 21:40:55 ON 23 JAN 2003

     FILE 'REGISTRY' ENTERED AT 21:42:48 ON 23 JAN 2003
L3                STRUCTURE UPLOADED
L4             2 S L3 SSS SAM
L5            17 S L3 SSS FULL

     FILE 'CAPLUS' ENTERED AT 21:43:36 ON 23 JAN 2003
L6            14 S L5
L7             0 S L6 AND (INHIBIT? OR ANTAGONIST?) AND (ANXIETY OR ANXIOUS? OR
L8             0 S L6 AND (ANXIETY OR ANXIOUS? OR ANXIOLY?)

     FILE 'STNGUIDE' ENTERED AT 21:45:33 ON 23 JAN 2003

     FILE 'REGISTRY' ENTERED AT 21:46:54 ON 23 JAN 2003
L9                STRUCTURE UPLOADED
L10           50 S L9 SSS SAM
L11         2061 S L9 SSS FULL

     FILE 'CAPLUS' ENTERED AT 21:47:23 ON 23 JAN 2003

=> s l11 and (anxiety or anxious? or anxioly?)
          1052 L11
          9325 ANXIETY
           395 ANXIOUS?
          7715 ANXIOLY?
L12         19 L11 AND (ANXIETY OR ANXIOUS? OR ANXIOLY?)

=> s l12 and mglur5(p)(antagonist? or inhibit?)
           460 MGLUR5
        189529 ANTAGONIST?
       1540801 INHIBIT?
           196 MGLUR5(P)(ANTAGONIST? OR INHIBIT?)
L13          2 L12 AND MGLUR5(P)(ANTAGONIST? OR INHIBIT?)
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=> s mglur5(p)(inhibit? or antagonist?) and (anxiety or anxious? or anxioly?)
          460 MGLUR5
      1540801 INHIBIT?
       189529 ANTAGONIST?
          196 MGLUR5(P)(INHIBIT? OR ANTAGONIST?)
         9325 ANXIETY
          395 ANXIOUS?
         7715 ANXIOLY?
L1         10 MGLUR5(P)(INHIBIT? OR ANTAGONIST?) AND (ANXIETY OR ANXIOUS? OR
              ANXIOLY?)

=> d l1 abs ibib kwic 1-10

L1   ANSWER 1 OF 10  CAPLUS  COPYRIGHT 2003 ACS
GI
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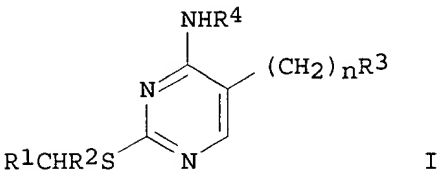

I

AB 4-Aminopyrimidines I [R1 = (un)substituted alkenyl, alkynyl, cycloalkyl, heteroaryl, alkoxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, cycloalkoxycarbonyl, cycloalkylmethoxycarbonyl, heteroarylmethoxycarbonyl; R, R4 = H, alkyl; R3 = (un)substituted aryl, heteroaryl, alkoxycarbonyl; n = 0-2] were prepd. for use in the prevention or treatment of **mGluR5** receptor mediated disorders. Thus, PhNhCH2CH2Cn was treated with PhCHO and the resulting acrylonitrile was cyclized with urea and treated with BrCH2CO2Et to give I [R1 = CO2Et, R2, R4 = H, R3 = Ph, n = 1] which had glutamate **antagonist** IC50 on rat mGlu 5a receptors of 0.14 .mu.M.

ACCESSION NUMBER: 2002:906173 CAPLUS
DOCUMENT NUMBER: 137:384860
TITLE: 4-Aminopyrimidines for treatment of mGluR5 receptor mediated disorders
INVENTOR(S): Mutel, Vincent; Peters, Jens-uwe; Wichmann, Juergen
PATENT ASSIGNEE(S): F. Hoffmann-La Roche Ag, Switz.
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002094795	A1	20021128	WO 2002-EP5379	20020516

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL,

PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,
UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: EP 2001-112564 A 20010523
OTHER SOURCE(S): MARPAT 137:384860
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB 4-Aminopyrimidines I [R1 = (un)substituted alkenyl, alkynyl, cycloalkyl, heteroaryl, alkoxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, cycloalkoxycarbonyl, cycloalkylmethoxycarbonyl, heteroarylmethoxycarbonyl; R, R4 = H, alkyl; R3 = (un)substituted aryl, heteroaryl, alkoxycarbonyl; n = 0-2] were prepd. for use in the prevention or treatment of **mGluR5** receptor mediated disorders. Thus, PhNhCH2CH2Cn was treated with PhCHO and the resulting acrylonitrile was cyclized with urea and treated with BrCH2CO2Et to give I [R1 = CO2Et, R2, R4 = H, R3 = Ph, n = 1] which had glutamate **antagonist** IC50 on rat mGlu 5a receptors of 0.14 .mu.M.

IT Analgesics
Anxiety
Anxiolytics
Glutamate **antagonists**
Human
Pain
(prepn. of 4-aminopyrimidines for treatment of **mGluR5** receptor mediated disorders)

L1 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2003 ACS
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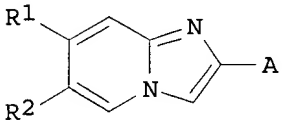

I

AB The title compds. [I; R1, R2 = H, alkyl, halogen, OH, alkoxy; A = (un)substituted aryl, heteroaryl, etc.], useful for the manuf. of medicaments for the treatment or prevention of GluR5 receptor mediated disorders, such as acute and/or chronic neurol. disorders, were prepd. and formulated. Thus, reacting 2-amino-4-chloropyridine with 3,4-dimethylphenacyl bromide in EtOH afforded 69% 7-chloro-2-(3,4-dimethylphenyl)imidazo[1,2-a]pyridine which showed IC50 of 0.1 .mu.M against mGluR 5a receptor binding.

ACCESSION NUMBER: 2002:888557 CAPLUS
DOCUMENT NUMBER: 137:384841
TITLE: Preparation of imidazo[1,2-a]pyridines as **mGluR5 antagonists**
INVENTOR(S): Mutel, Vincent; Peters, Jens-Uwe; Wichmann, Juergen
PATENT ASSIGNEE(S): F. Hoffmann-La Roche A.-G., Switz.
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002092086	A1	20021121	WO 2002-EP3098	20020320

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002188128	A1	20021212	US 2002-93790	20020308

PRIORITY APPLN. INFO.: EP 2001-107562 A 20010327

OTHER SOURCE(S): MARPAT 137:384841

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Preparation of imidazo[1,2-a]pyridines as **mGluR5 antagonists**

ST imidazopyridine prepn metabotropic glutamate 5 receptor **mGluR5 antagonist** analgesic

IT Nervous system
(Huntington's chorea, treatment of; prepn. of imidazo[1,2-a]pyridines as **mGluR5 antagonists**)

IT Nervous system
(amyotrophic lateral sclerosis, treatment of; prepn. of imidazo[1,2-a]pyridines as **mGluR5 antagonists**)

IT Mental disorder
(cognitive, treatment of; prepn. of imidazo[1,2-a]pyridines as **mGluR5 antagonists**)

IT Mental disorder
(depression, treatment of; prepn. of imidazo[1,2-a]pyridines as **mGluR5 antagonists**)

IT Nervous system
(disease, treatment of; prepn. of imidazo[1,2-a]pyridines as **mGluR5 antagonists**)

IT Cognition
(disorder, treatment of; prepn. of imidazo[1,2-a]pyridines as **mGluR5 antagonists**)

IT Glutamate receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic, **mGluR5**; prepn. of imidazo[1,2-a]pyridines as **mGluR5 antagonists**)

IT Analgesics
Anti-Alzheimer's agents
Anti-ischemic agents
Anticonvulsants
Antiparkinsonian agents
Antipsychotics
Anxiolytics
Cognition enhancers
Human
Nervous system agents
(prepn. of imidazo[1,2-a]pyridines as **mGluR5 antagonists**)

IT Mental disorder

(psychosis, treatment of; prepn. of imidazo[1,2-a]pyridines as **mGluR5 antagonists**)

IT Memory, biological
(retention defect, treatment of; prepn. of imidazo[1,2-a]pyridines as **mGluR5 antagonists**)

IT Mental disorder
(senile psychosis, treatment of; prepn. of imidazo[1,2-a]pyridines as **mGluR5 antagonists**)

IT Alzheimer's disease
Anxiety
Epilepsy
Ischemia
Multiple sclerosis
Pain
Parkinson's disease
Schizophrenia
(treatment of; prepn. of imidazo[1,2-a]pyridines as **mGluR5 antagonists**)

IT 885-91-6P 34658-67-8P 65964-60-5P 88965-00-8P 100965-76-2P
158959-20-7P 205655-15-8P 326018-20-6P 419557-33-8P 420832-11-7P
475992-33-7P 475992-34-8P 475992-35-9P 475992-36-0P 475992-37-1P
475992-38-2P 475992-39-3P 475992-40-6P 475992-41-7P 475992-42-8P
475992-43-9P 475992-44-0P 475992-45-1P 475992-46-2P 475992-47-3P
475992-48-4P 475992-49-5P 475992-50-8P 475992-51-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of imidazo[1,2-a]pyridines as **mGluR5 antagonists**)

IT 504-29-0, 2-Aminopyridine 695-34-1, 2-Amino-4-methylpyridine 1603-41-4
1835-02-5, 3,4-Dimethoxyphenacyl bromide 1835-12-7 2003-10-3
2227-64-7 2633-50-3, 3,4-Dimethylphenacyl bromide 4629-54-3
5000-65-7 10201-73-7, 2-Amino-4-methoxypyridine 10531-42-7
18523-22-3 19798-80-2, 2-Amino-4-chloropyridine 23489-36-3
26167-45-3 33252-32-3 39696-16-7 41011-01-2 51012-64-7
53631-18-8 61858-38-6 122654-17-5 151427-19-9 435273-49-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of imidazo[1,2-a]pyridines as **mGluR5 antagonists**)

L1 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2003 ACS

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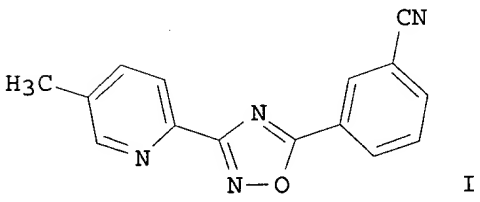

I

AB The invention provides compds. and pharmaceutical compns. that act as **antagonists** at metabotropic glutamate receptors, and that are

useful for treating neurol. diseases and disorders. Methods of prepg. the compds. also are disclosed. The compds. exhibit a high degree of potency and selectivity for individual metabotropic glutamate receptor subtypes, notably **mGluR5**. In particular, medical conditions assocd. with metabotropic glutamate receptors and therefore targeted by the invention compds. include stroke, head trauma, anoxic injury, ischemic injury, hypoglycemia, epilepsy, pain, migraine headaches, Parkinson's disease, senile dementia, Huntington's Chorea, and Alzheimer's disease. The invention provides methods of treating diseases assocd. with excitatory activation of an mGluR Group I receptor, and of **inhibiting** neuronal damage caused by excitatory activation of an mGluR Group I receptor, specifically wherein the mGluR Group I receptor is **mGluR5**. In one aspect of the invention, the **antagonists** may be represented by the general formula Ar1-L-Ar2, wherein Ar1 is an optionally substituted heteroarom. moiety, and Ar2 is an optionally substituted benzene ring. The L moiety is a group that not only covalently binds to the Ar1 and Ar2 moieties, and which facilitates adoption of the correct spatial orientation of Ar1 and Ar2, but also itself may interact with the protein, to effect receptor binding. In one embodiment of the invention, L is selected from the group consisting of -NH-, -S-, -O-, -CO-, -CONH-, -CONHCH2-, -CH2CONH-, -CNHNH-, -CNHNHCH2-, -C=NOCH2-, -CH2NHCH2-, -CH2CH2NH-, -NHCH2CO-, -NHCH2CHOH-, -NHCNHNH-, -NHCONH-, cyclopentane, cyclopentadiene, furan, thiofuran, pyrrolidine, pyrrole, 2-imidazoline, 3-imidazoline, 4-imidazoline, imidazole, pyrazoline, pyrazolidine, imidazolidine, oxazole, 2-oxazole, thiazole, isoxazole, isothiazole, 1H-1,2,4-triazole, 1H-1,2,3-triazole, 1,2,4-oxathiazole, 1,3,4-oxathiazole, 1,4,2-dioxazole, 1,4,2-oxathiazole, 1,2,4-oxadiazole, 1,2,4-thiadiazole, 1,2,5-oxadiazole, 1,2,5-thiadiazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1H-tetrazole, cyclohexane, piperidine, tetrahydropyridine, 1,4-dihydropyridine, pyridine, benzene, tetrahydropyran, 3,4-dihydro-2H-pyran, 2H-pyran, 4H-pyran, tetrahydrothiopyran, 3,4-dihydro-2H-thiopyran, 2H-thiin, 4H-thiopyran, morpholine, thiomorpholine, piperazine, pyridazine, pyrimidine, pyrazine, 1,2,4-triazine, 1,2,3-triazine, 1,3,5-triazine, and 1,2,4,5-tetrazine. In another embodiment of the invention, Ar1 is selected from the group consisting of Ph, benzyl, naphthyl, fluorenyl, anthrenyl, indenyl, phenanthrenyl, and benzonaphthenyl, and Ar2 is selected from the group consisting of thiazoyl, furyl, pyranyl, 2H-pyrrolyl, thienyl, pyrroyl, imidazoyl, pyrazoyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, benzothiazole, benzimidazole, 3H-indolyl, indolyl, indazoyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, phthalizinyl, naphthyridinyl, quinazolinyl, cinnolinyl, isothiazolyl, quinoxalinyl, indolizinyl, isoindolyl, benzothienyl, benzofuranyl, isobenzofuranyl, and chromenyl. Several hundred specific examples are individually prepd. and/or claimed. A variety of intermediates were also prepd. For instance, 5-methylpyrid-2-ylamidoxime was prepd. from 2-bromo-5-methylpyridine by Zn- and Pd-complex-mediated cyanation (56%) and reaction of the resulting nitrile with NH2OH.HCl (60%). Cyclization of the amidoxime with 3-cyanobenzoyl chloride (86%) gave invention compd. I. In a bioassay for **mGluR5** antagonism in primary astrocyte cultures from rats, the invention compds. had IC50 values in th range of 11 to 9140 nM.

ACCESSION NUMBER: 2002:676015 CAPLUS
DOCUMENT NUMBER: 137:201315
TITLE: Heteropolycyclic compounds, particularly pyridyl- and phenyl-substituted 1,2,4-oxadiazoles and analogs, and their use as metabotropic glutamate receptor antagonists for inhibiting neuronal damage
INVENTOR(S): Slassi, Abdelmalik; Van Wagenen, Bradford; Stormann,

Thomas M.; Moe, Scott T.; Sheehan, Susan M.; McLeod, Donald A.; Smith, Daryl L.; Isaac, Methvin Benjamin
PATENT ASSIGNEE(S): Can.
SOURCE: PCT Int. Appl., 272 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002068417	A2	20020906	WO 2002-US4689	20020219
WO 2002068417	A3	20021114		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-269847P P 20010221

AB The invention provides compds. and pharmaceutical compns. that act as **antagonists** at metabotropic glutamate receptors, and that are useful for treating neurol. diseases and disorders. Methods of prepg. the compds. also are disclosed. The compds. exhibit a high degree of potency and selectivity for individual metabotropic glutamate receptor subtypes, notably **mGluR5**. In particular, medical conditions assocd. with metabotropic glutamate receptors and therefore targeted by the invention compds. include stroke, head trauma, anoxic injury, ischemic injury, hypoglycemia, epilepsy, pain, migraine headaches, Parkinson's disease, senile dementia, Huntington's Chorea, and Alzheimer's disease. The invention provides methods of treating diseases assocd. with excitatory activation of an mGluR Group I receptor, and of **inhibiting** neuronal damage caused by excitatory activation of an mGluR Group I receptor, specifically wherein the mGluR Group I receptor is **mGluR5**. In one aspect of the invention, the **antagonists** may be represented by the general formula Ar1-L-Ar2, wherein Ar1 is an optionally substituted heteroarom. moiety, and Ar2 is an optionally substituted benzene ring. The L moiety is a group that not only covalently binds to the Ar1 and Ar2 moieties, and which facilitates adoption of the correct spatial orientation of Ar1 and Ar2, but also itself may interact with the protein, to effect receptor binding. In one embodiment of the invention, L is selected from the group consisting of -NH-, -S-, -O-, -CO-, -CONH-, -CONHCH2-, -CH2CONH-, -CNHNH-, -CNHNHCH2-, -C=NOCH2-, -CH2NHCH2-, -CH2CH2NH-, -NHCH2CO-, -NHCH2CHOH-, -NHCNHNH-, -NHCONH-, cyclopentane, cyclopentadiene, furan, thiofuran, pyrrolidine, pyrrole, 2-imidazoline, 3-imidazoline, 4-imidazoline, imidazole, pyrazoline, pyrazolidine, imidazolidine, oxazole, 2-oxazole, thiazole, isoxazole, isothiazole, 1H-1,2,4-triazole, 1H-1,2,3-triazole, 1,2,4-oxathiazole, 1,3,4-oxathiazole, 1,4,2-dioxazole, 1,4,2-oxathiazole, 1,2,4-oxadiazole, 1,2,4-thiadiazole, 1,2,5-oxadiazole, 1,2,5-thiadiazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1H-tetrazole, cyclohexane, piperidine, tetrahydropyridine, 1,4-dihydropyridine, pyridine, benzene, tetrahydropyran, 3,4-dihydro-2H-pyran, 2H-pyran, 4H-pyran,

tetrahydrothiopyran, 3,4-dihydro-2H-thiopyran, 2H-thiin, 4H-thiopyran, morpholine, thiomorpholine, piperazine, pyridazine, pyrimidine, pyrazine, 1,2,4-triazine, 1,2,3-triazine, 1,3,5-triazine, and 1,2,4,5-tetrazine. In another embodiment of the invention, Ar1 is selected from the group consisting of Ph, benzyl, naphthyl, fluorenyl, anthrenyl, indenyl, phenanthrenyl, and benzonaphthenyl, and Ar2 is selected from the group consisting of thiazoyl, furyl, pyranyl, 2H-pyrrolyl, thienyl, pyrroyl, imidazoyl, pyrazoyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, benzothiazole, benzimidazole, 3H-indolyl, indolyl, indazoyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, phthalizinyl, naphthyridinyl, quinazolinyl, cinnolinyl, isothiazolyl, quinoxalinyl, indolizinyl, isoindolyl, benzothienyl, benzofuranyl, isobenzofuranyl, and chromenyl. Several hundred specific examples are individually prepd. and/or claimed. A variety of intermediates were also prepd. For instance, 5-methylpyrid-2-ylamidoxime was prepd. from 2-bromo-5-methylpyridine by Zn- and Pd-complex-mediated cyanation (56%) and reaction of the resulting nitrile with NH2OH.HCl (60%). Cyclization of the amidoxime with 3-cyanobenzoyl chloride (86%) gave invention compd. I. In a bioassay for **mGluR5** antagonism in primary astrocyte cultures from rats, the invention compds. had IC50 values in th range of 11 to 9140 nM.

ST oxadiazole imidazole oxazole furan prepn **mGluR5** **antagonist**; heteropolycyclic phenylpyridyloxadiazole prepn metabotropic glutamate receptor **antagonist** neuroprotectant

IT Glutamate receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic, **mGluR5**; prepn. of pyridyl- and phenyl-substituted oxadiazoles and analogs as metabotropic glutamate receptor **antagonists** for **inhibiting** neuronal damage)

IT Analgesics
Anti-Alzheimer's agents
Anti-ischemic agents
Anticonvulsants
Antimigraine agents
Antiparkinsonian agents
Anxiolytics
Glutamate antagonists
Nervous system agents
Psychotropics
(prepn. of pyridyl- and phenyl-substituted oxadiazoles and analogs as metabotropic glutamate receptor antagonists for inhibiting neuronal damage)

IT Alzheimer's disease
Anxiety
Epilepsy
Hypoglycemia
Hypoxia, animal
Mental disorder
Pain
Parkinson's disease
(treatment of; prepn. of pyridyl- and phenyl-substituted oxadiazoles and analogs as metabotropic glutamate receptor antagonists for inhibiting neuronal damage)

L1 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2003 ACS

AB The selective and systemically active **antagonist** for the metabotropic glutamate receptor subtype 5 (**mGluR5**), 2-methyl-6-(phenylethynyl)pyridine (MPEP) was shown to display

anxiolytic-like activity in a no. of unconditioned assays of stress and **anxiety** (elevated plus maze, shock probe burying, marble burying, social interaction, and stress-induced hyperthermia) in rodents. In this report, we extend these observations found using unconditioned models of **anxiety** to include three models of conditioned **anxiety**, comparing the activity of MPEP to the clin. used **anxiolytics**, diazepam, and buspirone. MPEP and diazepam, but not buspirone, showed **anxiolytic**-like activity in the fear-potentiated startle (FPS) model. In a conditioned ultrasonic vocalization (USV) procedure, MPEP, diazepam, and buspirone reduced vocalizations to a similar degree. In the modified Geller-Seifter procedure, MPEP, diazepam, and buspirone displayed statistically significant **anxiolytic**-like activity, increasing the no. of punished responses. Thus, these findings confirm and extend previous reports that MPEP exhibits **anxiolytic**-like activity in rats, and suggests that development of **mGluR5 antagonists** may provide a novel approach to treating **anxiety** disorders.

ACCESSION NUMBER: 2002:512133 CAPLUS
TITLE: **Anxiolytic**-like activity of the **mGluR5 antagonist** MPEP. A comparison with diazepam and buspirone
AUTHOR(S): Brodkin, Jesse; Busse, Chris; Sukoff, Stacey J.; Varney, Mark A.
CORPORATE SOURCE: Merck Research Laboratories, San Diego, CA, 92121, USA
SOURCE: Pharmacology, Biochemistry and Behavior (2002), 73(2), 359-366
CODEN: PBBHAU; ISSN: 0091-3057
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI **Anxiolytic**-like activity of the **mGluR5 antagonist** MPEP. A comparison with diazepam and buspirone

AB The selective and systemically active **antagonist** for the metabotropic glutamate receptor subtype 5 (**mGluR5**), 2-methyl-6-(phenylethynyl)pyridine (MPEP) was shown to display **anxiolytic**-like activity in a no. of unconditioned assays of stress and **anxiety** (elevated plus maze, shock probe burying, marble burying, social interaction, and stress-induced hyperthermia) in rodents. In this report, we extend these observations found using unconditioned models of **anxiety** to include three models of conditioned **anxiety**, comparing the activity of MPEP to the clin. used **anxiolytics**, diazepam, and buspirone. MPEP and diazepam, but not buspirone, showed **anxiolytic**-like activity in the fear-potentiated startle (FPS) model. In a conditioned ultrasonic vocalization (USV) procedure, MPEP, diazepam, and buspirone reduced vocalizations to a similar degree. In the modified Geller-Seifter procedure, MPEP, diazepam, and buspirone displayed statistically significant **anxiolytic**-like activity, increasing the no. of punished responses. Thus, these findings confirm and extend previous reports that MPEP exhibits **anxiolytic**-like activity in rats, and suggests that development of **mGluR5 antagonists** may provide a novel approach to treating **anxiety** disorders.

L1 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2003 ACS

AB Metabotropic glutamate receptors (mGluR) are a family of eight suptypes of G-protein coupled receptors. Recently, MPEP (2-methyl-6-

(phenylethynyl)pyridine) was described as a subtype selective, potent **mGluR5 antagonist**. In vitro, MPEP was shown to interact with an allosteric binding site located in the transmembrane domain, independently from the glutamate binding site located in the large N-terminal domain. In vivo, profiling of MPEP suggests a therapeutic potential for **mGluR5 antagonists** in **anxiety** related disorders, inflammatory pain and drug dependence. MPEP was originally identified by chem. derivatization of two leads identified by high capacity screening at the human mGlu5 receptor, SIB-1757 (6-methyl-2-(phenazo)pyridin-3-ol) and SIB-1893 ((E)-2-methyl-6-(phenylethenyl)pyridine). Here, we describe the lead optimization process which led to the idendification of MPEP, as well as the SAR of this new class of **antagonists**. Examples will be given to illustrate the role of arom. substituents in the functional activity as well as in the binding affinity at the mGlu5 receptor.

ACCESSION NUMBER: 2002:190271 CAPLUS
TITLE: Structure activity relationships, receptor docking of phenylethynylpyridine derivatives, a series of selective non-competitive inhibitors of the mGlu5 receptor
AUTHOR(S): Gasparini, Fabrizio
CORPORATE SOURCE: Nervous System Research, Novartis Pharma AG, 4002 Basle, Switz.
SOURCE: Abstracts of Papers, 223rd ACS National Meeting, Orlando, FL, United States, April 7-11, 2002 (2002), MEDI-152. American Chemical Society: Washington, D. C.
CODEN: 69CKQP
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English

AB Metabotropic glutamate receptors (mGluR) are a family of eight suptypes of G-protein coupled receptors. Recently, MPEP (2-methyl-6-(phenylethynyl)pyridine) was described as a subtype selective, potent **mGluR5 antagonist**. In vitro, MPEP was shown to interact with an allosteric binding site located in the transmembrane domain, independently from the glutamate binding site located in the large N-terminal domain. In vivo, profiling of MPEP suggests a therapeutic potential for **mGluR5 antagonists** in **anxiety** related disorders, inflammatory pain and drug dependence. MPEP was originally identified by chem. derivatization of two leads identified by high capacity screening at the human mGlu5 receptor, SIB-1757 (6-methyl-2-(phenazo)pyridin-3-ol) and SIB-1893 ((E)-2-methyl-6-(phenylethenyl)pyridine). Here, we describe the lead optimization process which led to the idendification of MPEP, as well as the SAR of this new class of **antagonists**. Examples will be given to illustrate the role of arom. substituents in the functional activity as well as in the binding affinity at the mGlu5 receptor.

L1 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2003 ACS

AB Glutamate receptors play an essential role in fear-related learning and memory. The present study was designed to assess the role of the group I metabotropic glutamate receptor (mGluR) subtype 5 in the acquisition and retrieval of conditioned fear in rats. The selective **mGluR5 antagonist** 2-methyl-6-(phenylethynyl)-pyridine (MPEP) was applied systemically (0.0, 0.3, 3.0, 30.0 mg/kg per os) 60 min before the acquisition training and before the expression of conditioned fear, resp., in the fear-potentiated startle paradigm. MPEP dose-dependently blocked the acquisition of fear. This effect was not due to state-dependent

learning. MPEP also prevented the expression of fear at a dose of 30.0 mg/kg. As a pos. control for these effects, the authors showed that the benzodiazepine **anxiolytic** compd. diazepam (1.25 mg/kg i.p.) also blocked acquisition and expression of fear potentiated startle. MPEP did not affect the baseline startle magnitude, short-term habituation of startle, sensitization of startle by footshocks or prepulse **inhibition** of startle. These data indicate a crucial role for **mGluR5** in the regulation of fear conditioning. In the highest dose MPEP might exert **anxiolytic** properties.

ACCESSION NUMBER: 2001:502705 CAPLUS
DOCUMENT NUMBER: 135:236855
TITLE: The metabotropic glutamate receptor antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP) blocks fear conditioning in rats
AUTHOR(S): Schulz, B.; Fendt, M.; Gasparini, F.; Lingenhohl, K.; Kuhn, R.; Koch, M.
CORPORATE SOURCE: Animal Physiology, University of Tubingen, Tubingen, Germany
SOURCE: Neuropharmacology (2001), 41(1), 1-7
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Glutamate receptors play an essential role in fear-related learning and memory. The present study was designed to assess the role of the group I metabotropic glutamate receptor (mGluR) subtype 5 in the acquisition and retrieval of conditioned fear in rats. The selective **mGluR5** **antagonist** 2-methyl-6-(phenylethynyl)-pyridine (MPEP) was applied systemically (0.0, 0.3, 3.0, 30.0 mg/kg per os) 60 min before the acquisition training and before the expression of conditioned fear, resp., in the fear-potentiated startle paradigm. MPEP dose-dependently blocked the acquisition of fear. This effect was not due to state-dependent learning. MPEP also prevented the expression of fear at a dose of 30.0 mg/kg. As a pos. control for these effects, the authors showed that the benzodiazepine **anxiolytic** compd. diazepam (1.25 mg/kg i.p.) also blocked acquisition and expression of fear potentiated startle. MPEP did not affect the baseline startle magnitude, short-term habituation of startle, sensitization of startle by footshocks or prepulse **inhibition** of startle. These data indicate a crucial role for **mGluR5** in the regulation of fear conditioning. In the highest dose MPEP might exert **anxiolytic** properties.

IT **Anxiolytics**
Learning
(metabotropic glutamate receptor antagonist 2-methyl-6-(phenylethynyl)-pyridine MPEP blocks fear conditioning in rats)

IT Glutamate receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabotropic, **mGluR5**; metabotropic glutamate receptor **antagonist** 2-methyl-6-(phenylethynyl)-pyridine MPEP blocks fear conditioning in rats)

L1 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2003 ACS
AB A review, with 28 refs. Although multiple metabotropic glutamate (mglu) receptor subtypes were cloned in the early 1990s, progress in the characterization of these receptors has been slow because of difficulties

in obtaining subtype-selective ligands. However, in the past few years exciting progress has been made on the mglu5 receptor subtype following the identification of selective non-amino-acid-like ligands that implicate the mglu5 receptor as a potentially important therapeutic target, particularly for the treatment of pain and **anxiety**.

ACCESSION NUMBER: 2001:467137 CAPLUS
DOCUMENT NUMBER: 135:221343
TITLE: Novel allosteric antagonists shed light on mglu5 receptors and CNS disorders
AUTHOR(S): Spooren, W. P. J. M.; Gasparini, F.; Salt, T. E.; Kuhn, R.
CORPORATE SOURCE: Nervous System Research, Novartis Pharma AG, Basel, CH-4002, Switz.
SOURCE: Trends in Pharmacological Sciences (2001), 22(7), 331-337
CODEN: TPHSDY; ISSN: 0165-6147
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB A review, with 28 refs. Although multiple metabotropic glutamate (mglu) receptor subtypes were cloned in the early 1990s, progress in the characterization of these receptors has been slow because of difficulties in obtaining subtype-selective ligands. However, in the past few years exciting progress has been made on the mglu5 receptor subtype following the identification of selective non-amino-acid-like ligands that implicate the mglu5 receptor as a potentially important therapeutic target, particularly for the treatment of pain and **anxiety**.

IT Analgesics
Anxiolytics
(allosteric antagonists shed light on mGlu5 receptors and CNS disorders)

IT Glutamate **antagonists**
(**mGluR5**; allosteric **antagonists** shed light on mGlu5 receptors and CNS disorders)

IT Glutamate receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabotropic, **mGluR5**; allosteric **antagonists** shed light on mGlu5 receptors and CNS disorders)

L1 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2003 ACS

AB A review with 66 refs. is given. SIBIA and Novartis are investigating the use of excitatory amino acid agonists and **antagonists** for the metabotropic receptor and the ionotropic receptors AMPA and NMDA. Preliminary expts. indicate they may have potential in the treatment of epilepsy, stroke, **anxiety**, pain, and neurodegenerative disease. Methylphenylethynylpyridine (MPEP) is the lead compd. in the series. Other compds. in the series that arose from the collaboration were SIB-1893, and its equipotent analog, SIB-1757, both of which are subtype-selective, potent **antagonists** of **mGluR5**. Chem. derivation of SIB-1893 resulted in the discovery of MPEP, a selective, systemically active noncompetitive **mGluR5** **antagonist**. Studies using these agents have yielded data to support the involvement of **mGluR5** in inflammatory mech. hyperalgesia. MPEP is the most potent of these compds. with an IC50 value of 12 nM for **inhibition** of quisqualate-stimulated

phosphoinositide hydrolysis in recombinant human mGluR5a-expressing cells. MPEP exhibited no cross reactivity with mGluR1 and other mGluRs, or against representative NMDA, AMPA, and kainate receptors up to concns. of 100 .mu.M. The compd., administered orally (100 mg/kg) produced a 70% reversal of mech. hyperalgesia in the Freund's complete adjuvant model of inflammatory pain. By Oct. 1999, investigations with SIB-1757 and SIB-1893 had been discontinued in favor of MPEP.

ACCESSION NUMBER: 2000:903884 CAPLUS
DOCUMENT NUMBER: 135:13755
TITLE: Methylphenylethynylpyridine (MPEP)(Novartis)
AUTHOR(S): Micheli, Fabrizio
CORPORATE SOURCE: Glaxo Wellcome Medicines Research Centre, Verona, 37135, Italy
SOURCE: Current Opinion in Investigational Drugs (PharmaPress Ltd.) (2000), 1(3), 355-359
CODEN: COIDAZ
PUBLISHER: PharmaPress Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB A review with 66 refs. is given. SIBIA and Novartis are investigating the use of excitatory amino acid agonists and **antagonists** for the metabotropic receptor and the ionotropic receptors AMPA and NMDA. Preliminary expts. indicate they may have potential in the treatment of epilepsy, stroke, **anxiety**, pain, and neurodegenerative disease. Methylphenylethynylpyridine (MPEP) is the lead compd. in the series. Other compds. in the series that arose from the collaboration were SIB-1893, and its equipotent analog, SIB-1757, both of which are subtype-selective, potent **antagonists** of **mGluR5**. Chem. derivation of SIB-1893 resulted in the discovery of MPEP, a selective, systemically active noncompetitive **mGluR5** **antagonist**. Studies using these agents have yielded data to support the involvement of **mGluR5** in inflammatory mech. hyperalgesia. MPEP is the most potent of these compds. with an IC50 value of 12 nM for **inhibition** of quisqualate-stimulated phosphoinositide hydrolysis in recombinant human mGluR5a-expressing cells. MPEP exhibited no cross reactivity with mGluR1 and other mGluRs, or against representative NMDA, AMPA, and kainate receptors up to concns. of 100 .mu.M. The compd., administered orally (100 mg/kg) produced a 70% reversal of mech. hyperalgesia in the Freund's complete adjuvant model of inflammatory pain. By Oct. 1999, investigations with SIB-1757 and SIB-1893 had been discontinued in favor of MPEP.

IT Glutamate receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(AMPA-binding, antagonist; MPEP in treatment of epilepsy, stroke, **anxiety**, pain, and neurodegenerative disease)

IT Analgesics
Anti-ischemic agents
Anticonvulsants
Anxiolytics
(MPEP in treatment of epilepsy, stroke, **anxiety**, pain, and neurodegenerative disease)

IT Glutamate antagonists
(NMDA antagonists; MPEP in treatment of epilepsy, stroke, **anxiety**, pain, and neurodegenerative disease)

IT Glutamate receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(metabotropic, **mGluR5**, **antagonist**; MPEP in treatment of epilepsy, stroke, **anxiety**, pain, and neurodegenerative disease)

IT 96206-92-7, MPEP
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(MPEP in treatment of epilepsy, stroke, **anxiety**, pain, and neurodegenerative disease)

L1 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2003 ACS

AB Recently, selective and systemically active antagonists for the metabotropic glutamate 5 receptor (mGlu5) were discovered, and the most potent deriv. was found to be MPEP (2-methyl-6-(phenylethynyl)pyridine). Given the high expression of mGlu5 receptors in limbic forebrain regions, it was decided to evaluate the **anxiolytic** potential of MPEP. After an acute oral administration, MPEP attenuated the **anxiety**-dependent variable in a variety of well established **anxiety** test paradigms. In rats, MPEP (10, 30, and 100 mg/kg) increased punished responses in the Geller-Seifter test, but none of these effects reached statistical significance. MPEP significantly increased the ratio (open/total arm entries; 0.1, 1, and 10 mg/kg), the no. of open arm entries (0.1, 1, and 10 mg/kg), as well as time spent on open arm (0.1 and 1 mg/kg) in the elevated plus maze test. Furthermore, MPEP (0.3 and 1 mg/kg) significantly increased the time spent in social contact in the social exploration test. In mice, MPEP attenuated stress-induced hyperthermia (15 and 30 mg/kg) and decreased the no. of buried marbles in the marble burying test (7.5 and 30 mg/kg). Finally, MPEP (0.01, 0.1, 1, 10, and 100 mg/kg) was tested on spontaneous locomotor activity in mice, and only a dose of 100 mg/kg significantly reduced vertical activity; no effect was seen on horizontal activity. MPEP (7.5, 15, and 30 mg/kg) was ineffective on d-amphetamine-induced (2.5 mg/kg) locomotor activity in mice and prepulse inhibition in rats (1, 3, or 10 mg/kg). Thus, these findings indicate that MPEP exhibits **anxiolytic**-like effects and low risks for sedation and psychotomimetic side-effects in rodents.

ACCESSION NUMBER: 2000:846141 CAPLUS
DOCUMENT NUMBER: 134:36966
TITLE: **Anxiolytic**-like effects of the prototypical metabotropic glutamate receptor 5 antagonist 2-methyl-6-(phenylethynyl)pyridine in rodents
AUTHOR(S): Spooren, Will P. J. M.; Vassout, Annick; Neijt, Hans C.; Kuhn, Rainer; Gasparini, Fabrizio; Roux, Silvain; Porsolt, Roger D.; Gentsch, Conrad
CORPORATE SOURCE: Nervous System Research, Novartis Pharma AG, Basel, Switz.
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2000), 295(3), 1267-1275
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI **Anxiolytic**-like effects of the prototypical metabotropic glutamate receptor 5 antagonist 2-methyl-6-(phenylethynyl)pyridine in rodents

AB Recently, selective and systemically active antagonists for the

metabotropic glutamate 5 receptor (mGlu5) were discovered, and the most potent deriv. was found to be MPEP (2-methyl-6-(phenylethynyl)pyridine). Given the high expression of mGlu5 receptors in limbic forebrain regions, it was decided to evaluate the **anxiolytic** potential of MPEP. After an acute oral administration, MPEP attenuated the **anxiety** -dependent variable in a variety of well established **anxiety** test paradigms. In rats, MPEP (10, 30, and 100 mg/kg) increased punished responses in the Geller-Seifter test, but none of these effects reached statistical significance. MPEP significantly increased the ratio (open/total arm entries; 0.1, 1, and 10 mg/kg), the no. of open arm entries (0.1, 1, and 10 mg/kg), as well as time spent on open arm (0.1 and 1 mg/kg) in the elevated plus maze test. Furthermore, MPEP (0.3 and 1 mg/kg) significantly increased the time spent in social contact in the social exploration test. In mice, MPEP attenuated stress-induced hyperthermia (15 and 30 mg/kg) and decreased the no. of buried marbles in the marble burying test (7.5 and 30 mg/kg). Finally, MPEP (0.01, 0.1, 1, 10, and 100 mg/kg) was tested on spontaneous locomotor activity in mice, and only a dose of 100 mg/kg significantly reduced vertical activity; no effect was seen on horizontal activity. MPEP (7.5, 15, and 30 mg/kg) was ineffective on d-amphetamine-induced (2.5 mg/kg) locomotor activity in mice and prepulse inhibition in rats (1, 3, or 10 mg/kg). Thus, these findings indicate that MPEP exhibits **anxiolytic**-like effects and low risks for sedation and psychotomimetic side-effects in rodents.

ST methylphenylethynylpyridine **mGluR5 antagonist** **anxiolytic**

IT Behavior
(locomotor; **mGluR5 antagonist** 2-methyl-6-(phenylethynyl)pyridine exhibits **anxiolytic**-like effects with low risks for sedation and psychotomimetic side-effects in rodents)

IT **Anxiolytics**
Psychotomimetics
(**mGluR5 antagonist** 2-methyl-6-(phenylethynyl)pyridine exhibits **anxiolytic**-like effects with low risks for sedation and psychotomimetic side-effects in rodents)

IT Glutamate receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic, **mGluR5**; **mGluR5 antagonist** 2-methyl-6-(phenylethynyl)pyridine exhibits **anxiolytic**-like effects with low risks for sedation and psychotomimetic side-effects in rodents)

IT Mental activity
(sedation; **mGluR5 antagonist** 2-methyl-6-(phenylethynyl)pyridine exhibits **anxiolytic**-like effects with low risks for sedation and psychotomimetic side-effects in rodents)

IT 96206-92-7, 2-Methyl-6-(phenylethynyl)pyridine
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**mGluR5 antagonist** 2-methyl-6-(phenylethynyl)pyridine exhibits **anxiolytic**-like effects with low risks for sedation and psychotomimetic side-effects in rodents)

L1 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2003 ACS

AB The invention provides the use of selective **mGluR5** **antagonists** for the treatment of pain and **anxiety**, and the use of mGluR **antagonists** for the treatment of pain in which the analgesic effect is achieved by interaction of the **antagonists** primarily or predominantly at peripheral mGluR receptors.

09/821,416

ACCESSION NUMBER: 2000:240944 CAPLUS
DOCUMENT NUMBER: 132:246378
TITLE: **mGluR5** metabotropic glutamate receptor **antagonists** for the treatment of pain and **anxiety**
INVENTOR(S): Allgeier, Hans; Cosford, Nicholas David; Flor, Peter Josef; Gasparini, Fabrizio; Gentsch, Conrad; Hess, Stephen D.; Johnson, Edwin Carl; Kuhn, Rainer; Tricklebank, Mark; Urban, Laszlo; Varney, Mark Andrew; Velicelebi, Gonul; Walker, Katharine
PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.; Sibia Neurosciences Inc.
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000020001	A1	20000413	WO 1999-EP7239	19990930
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2345137	AA	20000413	CA 1999-2345137	19990930
AU 9961984	A1	20000426	AU 1999-61984	19990930
BR 9914215	A	20010703	BR 1999-14215	19990930
EP 1117403	A1	20010725	EP 1999-948905	19990930
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002526408	T2	20020820	JP 2000-573360	19990930
NO 2001001440	A	20010515	NO 2001-1440	20010321
US 2001056084	A1	20011227	US 2001-821416	20010329

PRIORITY APPLN. INFO.:
GB 1998-21503 A 19981002
US 1998-220813 A 19981223
WO 1999-EP7239 W 19990930

OTHER SOURCE(S): MARPAT 132:246378
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI **mGluR5** metabotropic glutamate receptor **antagonists** for the treatment of pain and **anxiety**

AB The invention provides the use of selective **mGluR5** **antagonists** for the treatment of pain and **anxiety**, and the use of mGluR **antagonists** for the treatment of pain in which the analgesic effect is achieved by interaction of the **antagonists** primarily or predominantly at peripheral mGluR receptors.

ST **mGluR5** metabotropic glutamate receptor **antagonist** pain; **anxiety mGluR5** metabotropic glutamate receptor **antagonist**

IT Nervous system

(central; **mGluR5** metabotropic glutamate receptor **antagonists** for the treatment of pain and **anxiety**)

IT Inflammation
(inflammatory pain; **mGluR5** metabotropic glutamate receptor **antagonists** for the treatment of pain and **anxiety**)

IT Analgesics
Anxiolytics
Biological transport
Blood-brain barrier
Drug delivery systems
(**mGluR5** metabotropic glutamate receptor **antagonists** for the treatment of pain and **anxiety**)

IT Glutamate receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabotropic, **mGluR5**; **mGluR5** metabotropic glutamate receptor **antagonists** for the treatment of pain and **anxiety**)

IT Glutamate receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabotropic, peripheral; **mGluR5** metabotropic glutamate receptor **antagonists** for the treatment of pain and **anxiety**)

IT Nerve, disease
(neuropathy, neuropathic pain; **mGluR5** metabotropic glutamate receptor **antagonists** for the treatment of pain and **anxiety**)

IT Drug delivery systems
(transdermal; **mGluR5** metabotropic glutamate receptor **antagonists** for the treatment of pain and **anxiety**)

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09/821,416

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=> d his

     (FILE 'HOME' ENTERED AT 21:37:18 ON 23 JAN 2003)

     FILE 'CAPLUS' ENTERED AT 21:37:27 ON 23 JAN 2003
L1            10 S MGLUR5(P)(INHIBIT? OR ANTAGONIST?) AND (ANXIETY OR ANXIOUS? O

     FILE 'REGISTRY' ENTERED AT 21:40:14 ON 23 JAN 2003
L2                STRUCTURE UPLOADED

     FILE 'STNGUIDE' ENTERED AT 21:40:55 ON 23 JAN 2003

     FILE 'REGISTRY' ENTERED AT 21:42:48 ON 23 JAN 2003
L3                STRUCTURE UPLOADED
L4             2 S L3 SSS SAM
L5            17 S L3 SSS FULL

     FILE 'CAPLUS' ENTERED AT 21:43:36 ON 23 JAN 2003

=> s l5
L6            14 L5

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       1540801 INHIBIT?
        189529 ANTAGONIST?
          9325 ANXIETY
           395 ANXIOUS?
          7715 ANXIOLY?
L7             0 L6 AND (INHIBIT? OR ANTAGONIST?) AND (ANXIETY OR ANXIOUS? OR
                 ANXIOLY?)

=> s l6 and (anxiety or anxious? or anxioly?)
          9325 ANXIETY
           395 ANXIOUS?
          7715 ANXIOLY?
L8             0 L6 AND (ANXIETY OR ANXIOUS? OR ANXIOLY?)
```

=> d l13 abs ibib kwic hitstr 1-2

L13 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS

AB A review with 66 refs. is given. SIBIA and Novartis are investigating the use of excitatory amino acid agonists and **antagonists** for the metabotropic receptor and the ionotropic receptors AMPA and NMDA. Preliminary expts. indicate they may have potential in the treatment of epilepsy, stroke, **anxiety**, pain, and neurodegenerative disease. Methylphenylethynylpyridine (MPEP) is the lead compd. in the series. Other compds. in the series that arose from the collaboration were SIB-1893, and its equipotent analog, SIB-1757, both of which are subtype-selective, potent **antagonists** of **mGluR5**. Chem. derivation of SIB-1893 resulted in the discovery of MPEP, a selective, systemically active noncompetitive **mGluR5** **antagonist**. Studies using these agents have yielded data to support the involvement of **mGluR5** in inflammatory mech. hyperalgesia. MPEP is the most potent of these compds. with an IC50 value of 12 nM for **inhibition** of quisqualate-stimulated phosphoinositide hydrolysis in recombinant human mGluR5a-expressing cells. MPEP exhibited no cross reactivity with mGluR1 and other mGluRs, or against representative NMDA, AMPA, and kainate receptors up to concns. of 100 .mu.M. The compd., administered orally (100 mg/kg) produced a 70% reversal of mech. hyperalgesia in the Freund's complete adjuvant model of inflammatory pain. By Oct. 1999, investigations with SIB-1757 and SIB-1893 had been discontinued in favor of MPEP.

ACCESSION NUMBER: 2000:903884 CAPLUS
DOCUMENT NUMBER: 135:13755
TITLE: Methylphenylethynylpyridine (MPEP)(Novartis)
AUTHOR(S): Micheli, Fabrizio
CORPORATE SOURCE: Glaxo Wellcome Medicines Research Centre, Verona, 37135, Italy
SOURCE: Current Opinion in Investigational Drugs (PharmaPress Ltd.) (2000), 1(3), 355-359
CODEN: COIDAZ
PUBLISHER: PharmaPress Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 66 refs. is given. SIBIA and Novartis are investigating the use of excitatory amino acid agonists and **antagonists** for the metabotropic receptor and the ionotropic receptors AMPA and NMDA. Preliminary expts. indicate they may have potential in the treatment of epilepsy, stroke, **anxiety**, pain, and neurodegenerative disease. Methylphenylethynylpyridine (MPEP) is the lead compd. in the series. Other compds. in the series that arose from the collaboration were SIB-1893, and its equipotent analog, SIB-1757, both of which are subtype-selective, potent **antagonists** of **mGluR5**. Chem. derivation of SIB-1893 resulted in the discovery of MPEP, a selective, systemically active noncompetitive **mGluR5** **antagonist**. Studies using these agents have yielded data to support the involvement of **mGluR5** in inflammatory mech. hyperalgesia. MPEP is the most potent of these compds. with an IC50 value of 12 nM for **inhibition** of quisqualate-stimulated phosphoinositide hydrolysis in recombinant human mGluR5a-expressing cells. MPEP exhibited no cross reactivity with mGluR1 and other mGluRs, or. . .

IT Glutamate receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(AMPA-binding, antagonist; MPEP in treatment of epilepsy, stroke,

anxiety, pain, and neurodegenerative disease)

IT Analgesics
Anti-ischemic agents
Anticonvulsants
Anxiolytics
(MPEP in treatment of epilepsy, stroke, **anxiety**, pain, and neurodegenerative disease)

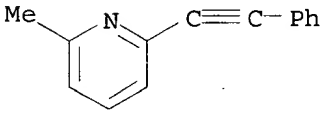
IT Glutamate antagonists
(NMDA antagonists; MPEP in treatment of epilepsy, stroke, **anxiety**, pain, and neurodegenerative disease)

IT Glutamate receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic, **mGluR5**, **antagonist**; MPEP in treatment of epilepsy, stroke, **anxiety**, pain, and neurodegenerative disease)

IT **96206-92-7**, MPEP
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(MPEP in treatment of epilepsy, stroke, **anxiety**, pain, and neurodegenerative disease)

IT **96206-92-7**, MPEP
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(MPEP in treatment of epilepsy, stroke, **anxiety**, pain, and neurodegenerative disease)

RN 96206-92-7 CAPLUS
CN Pyridine, 2-methyl-6-(phenylethynyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS

AB Recently, selective and systemically active antagonists for the metabotropic glutamate 5 receptor (mGlu5) were discovered, and the most potent deriv. was found to be MPEP (2-methyl-6-(phenylethynyl)pyridine). Given the high expression of mGlu5 receptors in limbic forebrain regions, it was decided to evaluate the **anxiolytic** potential of MPEP. After an acute oral administration, MPEP attenuated the **anxiety**-dependent variable in a variety of well established **anxiety** test paradigms. In rats, MPEP (10, 30, and 100 mg/kg) increased punished responses in the Geller-Seifter test, but none of these effects reached statistical significance. MPEP significantly increased the ratio (open/total arm entries; 0.1, 1, and 10 mg/kg), the no. of open arm entries (0.1, 1, and 10 mg/kg), as well as time spent on open arm (0.1 and 1 mg/kg) in the elevated plus maze test. Furthermore, MPEP (0.3 and 1 mg/kg) significantly increased the time spent in social contact in the social exploration test. In mice, MPEP attenuated stress-induced hyperthermia (15 and 30 mg/kg) and decreased the no. of buried marbles in the marble burying test (7.5 and 30 mg/kg). Finally, MPEP (0.01, 0.1, 1,

10, and 100 mg/kg) was tested on spontaneous locomotor activity in mice, and only a dose of 100 mg/kg significantly reduced vertical activity; no effect was seen on horizontal activity. MPEP (7.5, 15, and 30 mg/kg) was ineffective on d-amphetamine-induced (2.5 mg/kg) locomotor activity in mice and prepulse inhibition in rats (1, 3, or 10 mg/kg). Thus, these findings indicate that MPEP exhibits **anxiolytic**-like effects and low risks for sedation and psychotomimetic side-effects in rodents.

ACCESSION NUMBER: 2000:846141 CAPLUS
DOCUMENT NUMBER: 134:36966
TITLE: **Anxiolytic**-like effects of the prototypical metabotropic glutamate receptor 5 antagonist 2-methyl-6-(phenylethynyl)pyridine in rodents
AUTHOR(S): Spooren, Will P. J. M.; Vassout, Annick; Neijt, Hans C.; Kuhn, Rainer; Gasparini, Fabrizio; Roux, Silvain; Porsolt, Roger D.; Gentsch, Conrad
CORPORATE SOURCE: Nervous System Research, Novartis Pharma AG, Basel, Switz.
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2000), 295(3), 1267-1275
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

TI **Anxiolytic**-like effects of the prototypical metabotropic glutamate receptor 5 antagonist 2-methyl-6-(phenylethynyl)pyridine in rodents

AB . . . be MPEP (2-methyl-6-(phenylethynyl)pyridine). Given the high expression of mGlu5 receptors in limbic forebrain regions, it was decided to evaluate the **anxiolytic** potential of MPEP. After an acute oral administration, MPEP attenuated the **anxiety**-dependent variable in a variety of well established **anxiety** test paradigms. In rats, MPEP (10, 30, and 100 mg/kg) increased punished responses in the Geller-Seifter test, but none of. . . activity in mice and prepulse inhibition in rats (1, 3, or 10 mg/kg). Thus, these findings indicate that MPEP exhibits **anxiolytic**-like effects and low risks for sedation and psychotomimetic side-effects in rodents.

ST methylphenylethynylpyridine **mGluR5 antagonist** **anxiolytic**

IT Behavior
(locomotor; **mGluR5 antagonist** 2-methyl-6-(phenylethynyl)pyridine exhibits **anxiolytic**-like effects with low risks for sedation and psychotomimetic side-effects in rodents)

IT **Anxiolytics**
Psychotomimetics
(**mGluR5 antagonist** 2-methyl-6-(phenylethynyl)pyridine exhibits **anxiolytic**-like effects with low risks for sedation and psychotomimetic side-effects in rodents)

IT Glutamate receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic, **mGluR5**; **mGluR5 antagonist** 2-methyl-6-(phenylethynyl)pyridine exhibits **anxiolytic**-like effects with low risks for sedation and psychotomimetic side-effects in rodents)

IT Mental activity
(sedation; **mGluR5 antagonist** 2-methyl-6-(phenylethynyl)pyridine exhibits **anxiolytic**-like effects with low risks for sedation and psychotomimetic side-effects in rodents)

IT **96206-92-7**, 2-Methyl-6-(phenylethynyl)pyridine
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**mGluR5 antagonist** 2-methyl-6-(phenylethynyl)pyridine exhibits **anxiolytic**-like effects with low risks for sedation and psychotomimetic side-effects in rodents)

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RN 96206-92-7 CAPLUS
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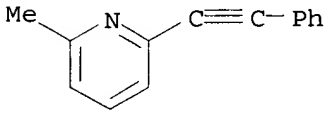

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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